American Journal of Hematology 54:267–270 (1997)

Failure of Pulse High-Dose Dexamethasone in Chronic Idiopathic Immune Thrombocytopenia

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Idiopathic thrombocytopenic purpura (ITP) is a disorder characterized by increased platelet destruction in the setting of normal megakaryopoiesis. Approximately 20% of patients with ITP are refractory to corticosteroids and splenectomy. Recently, pulse high-dose dexamethasone was reported to be effective in the treatment of chronic ITP in adult patients. We treated 9 patients with severe chronic ITP with monthly high-dose dexamethasone. None of the 9 patients responded with a sustained increase in platelet count. Five of these patients were unable to tolerate the regimen. The failure of high-dose dexamethasone in our hands contrasts with the good results of an earlier publication and suggests that there could be a subset of responders who will require better identification.
Am. J. Hematol. 54:267–270, 1997.

Key words: platelet; dexamethasone; thrombocytopenia

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is a disorder characterized by increased destruction of autoantibody-sensitized platelets, in the setting of normal megakaryopoeisis [1]. Clinical manifestations of ITP are due to the resulting thrombocytopenia and often reflect the degree of thrombocytopenia. Patients with mild to moderate ITP (platelet count from 50–150 $\times$ 10^9/l) usually have no bleeding symptoms, while those with severe thrombocytopenia (platelets count $<50 \times 10^9$/l) may experience mucosal bleeding, cutaneous purpura, or, rarely, life-threatening hemorrhage [2]. Treatment of ITP is usually reserved for those patients with severe thrombocytopenia or evidence of hemostatic dysfunction, such as petechiae or mucosal bleeding.

Corticosteroids, the first line of therapy in ITP, improve the platelet count in 70–80% of patients. Unfortunately, the majority of patients relapse when corticosteroids are withdrawn [3]. Patients who fail corticosteroids usually go on to have a splenectomy, a procedure that results in a rise in platelet count to safe levels in most ITP patients [4]. Twenty percent of ITP patients remain refractory to corticosteroids and splenectomy, and require more aggressive medical treatment. The choice of therapy for refractory patients is often a clinical dilemma, because each regimen has drawbacks such as unacceptable side effects [5]. Regimens include intermittent IVIgG [6], anti-rhesus globulin [7], immunosuppression with cyclophosphamide [8] or azathioprine [9], danazol [10], vinca alkaloids [11], and combination chemotherapy [12].

Recently, pulse high-dose dexamethasone was reported to be effective and well-tolerated in adult patients treated for refractory chronic ITP [13]. The regimen consisted of six monthly cycles of dexamethasone (40 mg), taken orally. Of 10 patients treated in this study, all responded with a sustained complete remission for the duration of follow-up, which ranged from 6–12 months. We used this therapy in 9 patients with refractory ITP. It was not successful in any of them.

PATIENTS AND METHODS

Selection of Patients

Six patients with chronic ITP were enrolled in the study from our outpatient hematology clinic. This was a

Contract grant sponsor: Canadian Red Cross Society Blood Services; Contract grant sponsor: Medical Research Council of Canada.

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Received for publication 29 June 1996; Accepted 6 November 1996.

prospective study investigating the usefulness of high-dose pulse dexamethasone. The study was approved by our ethics committee. The failure of the treatment in all entrants led to premature closure of the study. The diagnosis of ITP was based on the presence of thrombocytopenia, with normal bone-marrow megakaryocytes, the absence of splenomegally, and the absence of other causes of thrombocytopenia, such as systemic lupus erythematosus (SLE), lymphoproliferative diseases, or HIV. Three patients, who had received pulse high-dose dexamethasone in other centers, and who were subsequently referred to our outpatient clinic for management of chronic ITP, were included in the analysis. The diagnosis of ITP in these patients was based on the same criteria used in the selection of patients from our clinic. Information concerning their response to treatment and secondary effects was obtained from the original treating physician.

Treatment Regimen

The regimen consisted of 40 mg of oral dexamethasone given daily for 4 days at the beginning of each 28-day cycle [13]. Patients were seen 2 weeks after each cycle to assess their response and secondary effects. Six patients were already receiving treatment for severe thrombocytopenia (platelet count $<20 \times 10^9$/l) or for bleeding symptoms at the time of enrollment in the study. Concurrent treatments included prednisone, azathioprine, or intermittent IVIgG. During the study, none of the alternate treatments could be discontinued because of severe thrombocytopenia or ongoing bleeding symptoms. Patients were informed of potential side effects of dexamethasone including central nervous system effects, such as insomnia, anxiety, and dysphoria, and gastrointestinal symptoms such as bloating, heartburn, and weight gain. Written consent was obtained from all patients, and they were instructed to contact the outpatient department if they experienced unpleasant symptoms.

RESULTS

All patients fulfilled the criteria for the diagnosis of ITP.

Response to Therapy

Nine patients with chronic idiopathic thrombocytopenic purpura were treated with pulse high-dose dexamethasone. Their clinical characteristics are summarized in Table I. None showed a significant sustained increase in platelet count in response to dexamethasone. The mean platelet count (± SD) before and after completion of therapy was 12.9×10^9/l ($\pm 12.3 \times 10^9$/l) and 10.7×10^9/l ($\pm 7.5 \times 10^9$/l), respectively. Five patients (patients 1–4, 7, and 8) responded to at least one cycle of dexamethasone, with an increase in platelet count to $>50 \times 10^9$/l. In each of these patients, however, the platelet count fell back to baseline level or below, 7–10 days after completing a dexamethasone pulse. Patients 5, 6, and 9 had no response (platelet count $<20 \times 10^9$/l) to pulses of dexamethasone. There was no difference in response between patients who had previously had a splenectomy and those who had not. Four of the 9 patients developed complications and required additional treatment to raise their platelet count rapidly during dexamethasone treatment. Patient 8 developed vaginal bleeding, with a platelet count of 2×10^9/l. Patients 3, 5, and 6 were treated with IVIgG for severe thrombocytopenia and petechiae.

TABLE I. Patient Characteristics

Patient (no.), age/sex	Duration of disease (years)	Previous therapies	Concurrent therapy
(1) 46/F	21	Prednisone, splenectomy, vincristine, IVIgG, CHOP, cyclophosphamide	Nil
(2) 34/F	4	Prednisone	Prednisone
(3) 20/F	5	Predisone, IVIgG, anti-D, splenectomy, azathioprine	IVIgG
(4) 53/M	6	Prednisone, splenectomy, azathioprine, vincristine, danazol	Azathioprine
(5) 25/F	5	Prednisone, splenectomy, IVIgG, vincristine, danazol	IVIgG
(6) 28/F	23	Prednisone, IVIgG	Nil
(7) 66/F	7	Prednisone	Prednisone
(8) 42/F	0.75	Prednisone	Prednisone
(9) 77/F	11	Prednisone, splenic irradiation, splenectomy, vincristine, vitamin C, danazol, cyclophosphamide, anti-D, IVIgG	Nil

Secondary Effects

Six of 9 patients received fewer than six cycles of pulse dexamethasone. Dexamethasone was discontinued in patient 7 when she developed bleeding complications. In the other 5 patients, the decision to stop, pulse dexamethasone was based upon intolerance and lack of clinical response. The 5 patients were unable to continue on dexamethasone because of central nervous system side effects including insomnia, anxiety, and dysphoria. Other complaints included gastrointestinal symptoms (bloating and vomiting), alopecia, and vaginal yeast infections. Three patients completed all six cycles of therapy with minimal secondary effects. All side effects attributed to dexamethasone resolved after cessation of therapy.

Outcome of Patients

The outcomes of the patients in our series are summarized in Table II. One patient (patient 1) in our series died

TABLE II. Clinical Outcome of Patients

Patient (no.), age/sex	Platelet count prior to therapy ($\times 10^9$/l)	No. of cycles completed	Platelet count after therapy ($\times 10^9$/l)	Outcome
(1) 46/F	10	3	15	Deceased
(2) 34/F	15	6	15	Splenectomy
(3) 20/F	3	4	15	IVIgG
(4) 53/M	9	6	12	CNS hemorrhage
(5) 25/F	10	4	8	IVIgG
(6) 28/F	4	4	2	Splenectomy
(7) 66/F	42	5	24	Splenectomy
(8) 42/F	20	4	2	Prednisone
(9) 77/F	3	6	3	Danazol/IVIgG

of bleeding complications, 9 months after failing the dexamethasone treatment. Patient 4 suffered a right frontal hemorrhage 3 months following treatment, and was subsequently treated with cyclophosphamide and cyclosporine with a modest response. Each of the other 7 patients has remained a difficult management problem. Three patients had splenectomies after failing high-dose dexamethasone. All 3 responded initially to splenectomy, with elevations in their platelet counts to $>100 \times 10^9$/l. Unfortunately, only 1 of the 3 patients has maintained a partial remission postsplenectomy. Two patients relapsed within weeks of splenectomy and have been treated with cyclophosphamide or danazol. Patient 9 developed multiple complications including gastrointestinal bleeding and cellulitis. Two patients receive intermittent IVIgG to maintain acceptable platelet counts, and one continues on alternate-day prednisone.

DISCUSSION

The decision to treat chronic ITP depends on the degree of thrombocytopenia as well as the presence of a hemostatic defect [2]. The choice of treatment regimen is based on the expected clinical response, balanced against potentially harmful secondary effects. Pulse high-dose dexamethasone was recently reported to be effective in a small series of patients with chronic refractory ITP [13]. We evaluated this regimen in 9 patients with this disorder. All 9 patients had clinically severe ITP, characterized by marked thrombocytopenia and the presence of bleeding symptoms. The patients had failed a mean of four treatment regimens before this study, including 5 patients who had already failed splenectomy. Unfortunately, in response to pulse dexamethasone, none of the 9 patients had a sustained increase in their platelet count. Four patients required additional treatment for severe thrombocytopenia during dexamethasone therapy, and 6 did not complete the six cycles of treatment because of poor tolerance.

The poor response to pulse high-dose dexamethasone in this series contrasts with the results reported previously using this regimen [13]. This disparity may be partially explained by the selection of patients for this study. For example, the mean duration of illness for patients in our series (9 years) was over twice as long as the mean duration of illness for patients reported by Andersen [13] (4 years). Patients with a more prolonged disease course and multiple exposures to corticosteroids may be less sensitive to dexamethasone. Three of our patients had no response to dexamethasone, suggesting they were refractory to corticosteroids. An additional explanation may be that many of the patients in this series did not receive the full six cycles of dexamethasone. However, it seems unlikely that the patients in whom therapy was discontinued would have responded eventually, as none had shown an increase in platelet count after 3–4 cycles of dexamethasone. Lastly, 6 of our patients were receiving concurrent therapy during the period of study and this may have affected their response to dexamethasone. Alternatively, the need for concurrent therapy may simply reflect severe disease in our patients, making them less likely to respond to any treatment.

To date, reports on the use of high-dose dexamethasone have appeared only in abstract form. Young et al. [14] treated 10 adults with chronic ITP with pulse high-dose dexamethasone and observed only one sustained complete response. Four patients in their series were unable to complete six cycles of dexamethasone because of poor tolerance. The best results were observed in pediatric patients. Out of a total of 28 patients, 9 responded with persistently elevated platelet counts for periods of up to 1 year [15,16]. However, pediatric patients are more likely to have spontaneous remission of ITP than adults.

In summary, we report the failure of pulse high-dose dexamethasone in the treatment of 9 adults with chronic ITP. We observed no difference in response to dexamethasone between those patients who had previously had a splenectomy and those who had not. Consequently, our data suggest that splenectomy should not be delayed in order to assess the response to this treatment. The poor response to dexamethasone observed in this series may have been due to the selection of patients with longstanding, severe disease, which in some cases was refractory to corticosteroids. There may be a subgroup of patients with ITP who are sensitive to pulse dexamethasone. Further characterization of patients' response to this regimen may allow better definition of this subgroup.

ACKNOWLEDGMENTS

This work was supported by the Canadian Red Cross Society Blood Services through a Clinical Fellowship

Award (M.W.) and by a grant from the Medical Research Council of Canada (J.G.K.).

REFERENCES

1. Kiefel V, Santoso S, Mueller-Eckhardt C: Serological, biochemical, and molecular aspects of platelet autoantigens. Semin Hematol 29:26–33, 1992.
2. Warkentin TE, Kelton JG: Current concepts in the treatment of immune thrombocytopenia. Drugs 40:531–542, 1990.
3. Waters AH: Autoimmune thrombocytopenia: Clinical aspects. Semin Hematol 29:18–25, 1992.
4. Berchtold P, McMillan R: Therapy of chronic idiopathic thrombocytopenic purpura in adults. Blood 74:2309–2317, 1989.
5. Manoharan A: Treatment of refractory idiopathic thrombocytopenic purpura in adults. Br J Haematol 79:143–147, 1991.
6. Bussel JB, Pham LC, Aledort L, Nachman R: Maintenance treatment of adults with chronic refractory immune thrombocytopenic purpura using repeated intravenous infusions of gammaglobulin. Blood 72: 121–127, 1988b.
7. Mueller-Eckhardt C, Salama A: Anti-Rh(D) immunoglobulin for immune thrombocytopenic purpura. Lancet 2:50, 1986.
8. Pizzuto J, Ambriz R: Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric trial of the Cooperative Latin American Group on Hemostasis and Thrombosis. Blood 64:1179–1183, 1984.
9. Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ: Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura. Br J Haematol 74:223–228, 1990.
10. Ahn YS: Efficacy of danazol in hematologic disorders. Acta Haematol (Basel) 84:122–129, 1990.
11. Ahn YS, Harrington WJ, Seelman RC, Eytel CS: Vincristine therapy of idiopathic and secondary thrombocytopenias. N Engl J Med 291: 376–380, 1974.
12. Figueroa M, Gehlsen J, Hammond D, Ondreyco S, Piro L, Pomeroy T: Combination chemotherapy in refractory immune thrombocytopenic purpura. N Engl J Med 328:1226–1229, 1993.
13. Andersen J: Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. N Engl J Med 330: 1560–1564, 1994.
14. Young RR, Marchioli CC, Basmajian JH, Cherny RC, Loughran TP, Himpler BS: Pulse high-dose dexamethasone therapy in patients with idiopathic thrombocytopenic purpura. Blood 85:252, 1995 (abstract).
15. Nugent D, Hawkins D, Pendergrass T, Tarantino M: Long term follow up of refractory immune mediated thrombocytopenic purpura (ITP) patients treated with high dose dexamethasone therapy (dex.). Blood 85:250, 1995 (abstract).
16. Moertel CL, Smith C, Nelson S, Hilden J: Lack of a sustained response to high dose dexamethasone therapy (dex) in children with chronic immune-mediated thrombocytopenic purpura (ITP). Blood 85:251, 1995 (abstract).